Biosimilars
within the new Spanish National Health System

Proposals for action

February 2022

BioSim
Asociación Española de Biosimilares

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Overview

Between 2020 and 2021, many institutions, both national and European, have repeatedly highlighted the need to promote the use of biosimilars in order to maximize the opportunities these therapies represent as a tool to optimize pharmaceutical expenditure within the Spanish national health system.

The Opinion of Spain's Commission for Economic and Social Reconstruction of the Congress of Deputies[1] specifically mentions the need to implement an active policy for promoting the use of generics and biosimilars. On its part, the Independent Authority for Fiscal Responsibility (AIReF), in its Study of Hospital Pharmaceutical Expenditure within the Spanish national health system[2], highlights "the use of biosimilars to replace reference biologic drugs, both when initiating treatment for new patients and when exchanging treatment for patients already receiving a reference biological drug" as the most relevant and important proposal for making progress in the rational use of drugs. In order to achieve this, AIReF proposes measures that encourage prescription of biosimilars, provide legal protection for professionals when making decisions on switching from one drug to another, promote the use of open procurement procedures (framework agreements, etc.) and ensure that healthcare professionals and patients have accurate information on biosimilars.

In addition to these recommendations, the European Pharmaceutical Strategy[3] calls for maximizing the potential savings derived from the use of biosimilars and for a more widespread use of biosimilars by healthcare services.

To this end, it is proposed, among other measures, to review pharmaceutical regulations for biosimilars, including

exchangeability, as well as to share best practices among member countries. In any case, it must be noted that, in Europe there are different models of healthcare systems and therefore, measures have to be adapted to the particular characteristics of each country.

The Spanish Government, in the draft of the "Action Plan to promote the use of market-regulating drugs within the Spanish national health system: biosimilars and generic drugs"[4], prepared by the Ministry of Health, also includes the need to promote biosimilar use by implementing actions throughout the entire process, from authorization to prescription and dispensing of the drug.

However, beyond the clear aim of all institutions and administrations involved, there is a lack of clear, concrete, sufficiently defined and measurable proposals to achieve the successful establishment of biosimilars within the Spanish national health system.

For this reason, in order to address, discuss and prioritize a set of specific proposals that can be implemented within the Spanish healthcare system in order to promote biosimilar use at different levels of pharmaceutical provision and pharmaceutical policy management, from the macro to the micro level, BioSim proposed to bring together a multidisciplinary working group comprised by experts from clinical practice, pharmacy, pharmaceutical policy management, health economics, as well as patient representatives (Annex I). The members of the working group and the methodology used are shown in Annexes I and II of this document.

Section 1

Research, development and manufacturing of biosimilars

The COVID-19 pandemic has put to the test all healthcare systems, including the Spanish national health system. One of the lessons learned from this health crisis has been the importance of having a strong, competitive, specialized and sustainable European drug sector. Depending on third parties (mainly India and China) for manufacturing drugs puts Europe at risk of future crises. Off-patent drugs, such as biosimilars, have demonstrated the importance of having a greater number of alternatives to avoid potential shortages.

Similarly, in the research and development stage, Spain has very little presence in clinical trials with biosimilars; even the clinical phase of investigational biosimilars that are being developed in Spain is conducted outside Spain.

Since a large number of biological molecules will go off patent in the next four or five years, the current supply of biosimilars on the market is expected to grow exponentially. For this reason, clinical research with biosimilars will become ever more necessary.

Regulatory requirements for evaluation of biosimilars are very strict, and prior to market entry, biosimilars must undergo appropriate clinical development. However, it should be noted that there is a discussion regarding the need to conduct clinical trials on all new biosimilars[5,6] and, in fact, some state agencies, such as the British agency, have revised their guidelines in this regard[7].

In any event, as long as the requirements remain as they currently are, hospitals and research sites from the Spanish national health system can participate in these clinical trials. Likewise, encouraging the conduction of clinical trials with biosimilars in Spain may be a good way of facilitating the introduction of biosimilars in the clinical practice, especially in therapeutic areas where biosimilar use is not significant yet, such as ophthalmology or neurology. Furthermore, we must not forget that clinical trials are an opportunity to provide early access to biological therapies for many patients.

In this context, the expert panel was asked how incentives may be established in Spain for the research and manufacturing of biosimilars. Following the discussion, the experts recommend the following proposals for action:

1.
Establishing specific incentives for biosimilar companies through public programmes aimed at romoting competition among companies within the sector.

It is proposed to specify two types of aid, which may be linked to the PROFARMA plan or to research aid from the various ministries involved:

- R&D incentives to encourage the development of new biosimilar molecules.
- Incentives for the production and manufacturing of biosimilars in Spain, linked to the commitment for the production of these drugs in sites located across Spain.

2.
Implementing actions to promote clinical research with biosimilars

In order to accomplish this goal, the following is proposed:

- To involve medium-sized hospitals or sites with small clinical trial units in the development and strengthening phase, although with the necessary resources to advance them, during the implementation of pre-marketing clinical research (phase I, II and III) studies. To this end, it may be necessary to identify those molecules that are being developed and to contact sites and hospitals through regional managers.

- To promote the development of phase IV post-marketing studies that provide real-world evidence on the safety and efficacy of biosimilars in different therapeutic areas. These real-world data are in great demand by clinicians and may be very useful in advancing aspects such as confidence in biosimilars, exchangeability with the reference biological drug, as well as to increase knowledge on health outcomes. It must be noted, however, that managers of drug evaluation bodies within Europe claim that systematic exchangeability studies are not necessary[8]. In any event, these studies may be financed and led by the public sector (Ministry of Health through the AEMPS or the Carlos III Institute), as it has already been the case in other countries (NOR-Switch study[9] in Norway).

- To involve Scientific Societies such that, with the involvement of their cooperative groups, this type of work can be developed in the real world, involving a significant sample of patients. To make these studies more feasible and to give them greater credibility, public/private funds can be applied for or multiple sponsorship may also be used. The use of existing sources of information, such as computerized primary care medical records or already created databases, such as BIOBADASER or other similar databases, may also be considered.

- To involve central services of regional health services, so that research foundations from most Autonomous Communities of Spain can be involved to coordinate research resources and to allow participation of a greater number of hospitals within the same Autonomous Community.

Section 2

Use of biosimilars within the Spanish national health system

This section covers different aspects related to biosimilar use in the clinical practice within the Spanish national health system. Among other aspects, all recommendations implemented by organizations such as the AIReF, which proposes incorporating a set of goals related to biosimilar use in all management contracts for health areas or departments with the corresponding regional service, are taken into consideration[2].

In this regard, there are experiences in other countries within our sector. For example, the French government, in its Strategy for 2018-2022 Health, has set a target of 80% penetration for biosimilars in 2022, expressed as biosimilar use in terms of total active ingredient[10].

In any event, it is a challenging task to collect data on biosimilar use, whether at the national, regional or even hospital level.

It can be challenging to manage any project for change if we do not know the starting point and which goal we want to achieve. Countries with healthcare systems similar to the Spanish healthcare system, such as the United Kingdom or Italy, publish detailed data on biosimilar use for each healthcare departments. This information allows discussion of the data in terms of variability in the use of different drugs, level of penetration in the different regions, and even average acquisition price[11]. In Spain, some Autonomous Communities have made progress in this by publishing aggregate data in their health observatories[12,13].

In Spain, there are no national incentives to promote the use of biosimilars. Only at the regional or hospital level do some sites use biosimilars, although according to the AIReF report[2], this is not common practice and the few sites that do use them do so only locally, occasionally and with very little impact on the total incentive weight.

On the other hand, in countries close to Spain, incentives for the prescription of biosimilars at

different levels (national, regional or local) have been shown to increase rates of biosimilar use[14]. These initiatives, such as gainsharing schemes, encourage prescription and allow achieving a set of incentives, financial or otherwise, depending on whether the prescribing targets previously set are achieved. These are shared gains, since part of the savings obtained revert back to the health service/hospital itself, allowing the acquisition of technology, training or hiring of additional resources, among other things.

However, in order for biosimilars to achieve an adequate market penetration, a broad consensus regarding criteria for biosimilar use must be reached among clinicians.

The use of biosimilars in naïve patients (new patients or patients initiating biologic therapy) does not raise concerns among the scientific community and should be the first strategy to promote biosimilar use within the Spanish national health system that may be proposed by the Ministry of Health. This strategy is actually being implemented in many Autonomous Communities of Spain. However, for patients that are already following treatment, also known as continuation therapy,

where prescribing a biosimilar involves changing the trade name of the biological therapy that the patient is already receiving, i.e., making a change or switch, concerns may arise. Although the scientific evidence shows similar efficacy and safety data after switching[8,15], this change continues to generate reticence, which is increased due to the prospect of frequent changes in treatment (multiswitch).

In this regard, some countries have gone a step further by establishing national positioning on exchangeability or even implementing switch programmes at different levels. For example, the Italian Medicines Agency, in its Second Position Paper on Biosimilars, established that biosimilars and original biological drugs are considered exchangeable in both naïve patients and those that follow an established treatment[16.] Something similar occurs with positioning by the Norwegian Medicines Agency[17] regarding exchangeability between original drugs and biosimilars.

On their part, several hospitals in the United Kingdom have experiences of a switching programme managed by a multidisciplinary team, which demonstrates the safety and efficacy of the switch. One example reported in the literature is the experience in the Southampton Hospital[18].

On the other hand, six Canadian provinces (Alberta, Ontario, British Columbia, New Brunswick and Quebec) have already implemented mandatory switch programmes to switch from original drugs to biosimilars[19,20.]

After the different needs and experiences were submitted to the expert panel for consideration, the following set of measures aimed at encouraging the use of biosimilars was suggested:

1.
To urge health administrations to collect and report indicators on biosimilar use at the central, regional, provincial or hospital level.

These indicators, differentiated for hospital-acquired products and products dispensed by prescription, should be public and consistent in their construction. This way, management can be improved by sharing best practices among hospitals or Autonomous Communities of Spain. This initiative, promoted by the Autonomous Communities of Spain, should be coordinated by the Pharmacy's Standing Committee of the Spanish national health system. The publication of these indicators will stimulate the strategy for promoting biosimilars.

2.
To establish a target percentage for the use of biosimilars at the national level and by Autonomous Community.

This percentage may be set as a whole for all biosimilars or individually for each biosimilar. In the latter case, it should be customized according to the length of time the molecule has been on the market, so that the target figure can be adapted to the level of penetration achieved by each biosimilar.

Ideally, these targets may need to be customized for each site, so that these can be adapted to all contexts and encourage biosimilar use in all contexts.

Establishing and promoting the use of biosimilars does not undermine the freedom of prescription by the physician, who will always be able to choose the drug that he/she deems the most appropriate, taking into account both the clinical state of the patient and the efficiency criteria of the organization.

3.
To implement some type of collective direct incentive to clinical services/hospitals as a measure that promotes biosimilar use.

Although this proposal is difficult to implement, the possibility of establishing direct incentives for those clinical services/hospitals that, for example, reach the pre-established target for biosimilar use, make an above-average use of biosimilars or show a greater growth in the percentage of biosimilar use, should be assessed.

One option that may be evaluated is linking this incentive programme to participation in research projects, clinical trials or the aforementioned phase IV studies.

4.
To promote the implementation of gainsharing schemes by regional health systems.

There are no references to the implementation of gainsharing schemes in Spain. Based on the experiences of other countries, it seems that these actions may benefit greatly the promotion of biosimilar use with a model that produces benefits for the administration, professionals and patients.

It may be advisable to conduct, as a matter of urgency, pilot experiences with this type of models to assess their feasibility and efficiency in Spain.

The experts consider that it may necessary to involve the Ministry of Finance (Hacienda) and Health Departments[21] in this model, such that part of the funds obtained from the application of the sixth additional provision of the Law on Guarantees and Rational Use of Medicines may be used for its implementation. Thus, in addition, the outcome of these experiences may be reported to the Interterritorial Council prior to approving the use of funds by the Council of Ministers and the outcome of the projects could be assessed.

5.
To urge Scientific Societies, Health Technology Assessment Agencies and Health Services to update the therapeutic strategies included in the Clinical Practice Guidelines when a new biosimilar molecule is introduced.

In addition to incorporating into therapeutic strategies all molecules approved for the treatment of a pathology, it must be noted that the benefit/cost ratio is taken into account when establishing the therapeutic positioning of a drug. Based on this ratio, the disease state where use of the biosimilar is most efficient is established. Marketing of biosimilars modifies this ratio by allowing the same health outcomes at a lower cost, so there is a possibility that the therapeutic positioning may vary and that treatment options with biological drugs may be provided to a greater number of patients. This is what has happened in the UK national health system (NHS), where marketing for anti-TNF biosimilars has resulted in the NICE modifying treatment guidelines for rheumatoid arthritis, from recommending the use of biological drugs only in severe cases to recommending the use of biological drugs also in cases of moderate arthritis. This has resulted in thousands of new patients to benefit from biosimilars[22].

6.
To urge the Spanish Agency of Medicines and Medical Devices (AEMPS) to make a pronouncement on the safety of the exchange between biological molecules.

It may be advisable for the regulatory body to establish clear criteria on exchangeability, so that the administrations can publish recommendations on biosimilar use, both in naïve patients and in patients already on treatment, in collaboration with the Scientific Societies and with the participation of Patients' Associations.

7.
To encourage the conduction and publication of studies on health outcomes for biosimilars,

including results on adherence, patient progress, quality of life and side effects.

Section 3

Public procurement and dispensing of biosimilars

Once the exclusivity of patent rights has expired, public procurement processes for biological drugs, for which there is competition, must promote competitive procurement procedures in order to adapt to the Public Sector Contracts Law[2]. For this reason, open procedures are typically used and rationalization models, such as "framework agreements" with supplier approval and single batches per active ingredient, can be applied. Delays in the implementation of these procedures have been identified as a hurdle to the entry of biosimilars[23]. In Italy, in order to promote the use of biosimilars, procedure for their procurement has been statutorily regulated[24] (procurement model, period for organizing the procurement process, number of suppliers, etc.).

With regard to community pharmacies, there are currently few biosimilars available in pharmacies (chondroitin sulfate, enoxaparin sodium, insulin glargine, follitropin alfa and teriparatide), although some of them, such as insulin glargine, are widely used. However, this number is likely to increase in the short term, and no procedure has yet been established to encourage dispensing of biosimilars by pharmacies, although in the current Spanish legal framework, prescription by brand name guides dispensing. In order to alleviate this lack of incentive for the use of biosimilars within the primary care setting, France has established incentives for the dispensing of biosimilars[25], similar to what happened in Spain during the first stage of marketing for generic drugs. In this same area, there is also no incentive for patients to value the dispensing of biosimilars and to understand the guarantees in terms of quality, safety and efficacy provided by biosimilars, as well as the greater efficiency associated with their use.

In this area, the expert panel considers that it may be appropriate to establish the following proposals for action:

1.
To extend and regulate the use of the framework agreement as a procurement procedure, with approval and allocation to different suppliers,

being a procedure that ensures competition and concurrence. A greater number of suppliers guarantees supply and allows the clinician to customize and select the treatment that best suits the clinical characteristics of a patient. One aspect that may accelerate these agreements is the availability of sufficient and rapid information on drugs that will go off-patent or that will be marketed in the coming months20, so that procurement specifications can be prepared sufficiently in advance. In addition, procedures that allow for the review of awarded contracts must be developed. This way, contracts can be adapted to the entry of new competition, taking into account the need for stability required by the supplier along with the purchasing flexibility that is essential for the contracting body.

2.
To evaluate implementation of measures that promote prescription of biosimilars within primary health settings in those therapeutic areas for which there are biosimilar biological molecules on the market.

These actions will become progressively more relevant as the number of biosimilars dispensed in pharmacies increases, as an additional tool to promote biosimilar use within the Spanish national health system.

Section 4

Training and dissemination of knowledge on biosimilars

Generating knowledge on biosimilars continues being one of the targets that must be addressed, in terms of training healthcare professionals, patients and the society as a whole.

A recent review showed that, in Spain, there are still many knowledge "gaps" among physicians and pharmacists, both in hospital and community settings, regarding biosimilars[26,27]. Likewise, a recent study[28] highlighted the lack of knowledge on biosimilars by the patients, something that is the root cause of the lack of confidence in these therapies.

To address these needs, experts suggest doing the following:

1.
To conduct outreach campaigns on biosimilars aimed at patients by the national and regional bodies accredited for this purpose.

A very successful precedent was the outreach campaign on generic drugs conducted in Spain in 2010[29]. On its part, the Australian government has been the first leading an outreach campaign on biosimilars[30], which may be used as a model.

2.
To involve Scientific Societies in the generation and dissemination of content through organized and protocolized training programmes aimed at professionals, with special emphasis on guarantees in terms of quality, safety and efficacy of biosimilars.

These programmes should particularly focus on those therapeutic areas with less experience in biosimilar use, such as ophthalmology, dermatology, neurology and oncology, where these therapies may grow significantly in the coming years.

This training should also focus on the primary care setting, where this type of therapies are less common, since biosimilars have been traditionally used in hospital settings. On a survey conducted in 2018 in Spain on more than 700 healthcare professionals, 58% of respondents did not know the definition of biosimilar and 73% did not know that management of biosimilars is not comparable to that of generics, which in Spain are prescribed based on active ingredient[27].

3.
To develop training programmes for patients, channelled through health schools, with the i nvolvement of Patients' Associations and Scientific Societies, that contribute to truly implement shared decision-making between clinicians and patients.

This information should address the concepts of drug efficiency and cost, as this may help society to understand the economic impact on sustainability and its value for the Spanish national health system; however, these concepts should be accompanied by information on the quality, safety and efficacy of biosimilars.

Proposals to encourage the use of biosimilars within the Spanish national health system

1. To establish **specific incentives for biosimilar companies through public programmes** aimed at promoting competition among companies within the sector, both to encourage development of new biosimilar molecules and manufacturing of biosimilars in Spain.

2. To implement actions that promote **clinical research with biosimilars**, focusing on implementation of post-marketing studies that produce real-world data, with the collaboration of Scientific Societies, regional health systems and the participation of different sites and sponsors.

3. To urge the central Administration and the Autonomous Communities of Spain to **collect and publish indicators on biosimilar use at both the community and hospital level**. These indicators should be differentiated for hospital drugs and drugs dispensed by prescription.

4. To establish a **target percentage of biosimilar use at the national level and by Autonomous Community of Spain**. This percentage should be different for each molecule and for each site, and it should be based on growth against data achieved in the previous period.

5. To consider the **implementation of any type of incentive for clinical services/hospitals/professionals** as a measure that encourages biosimilar use. This incentive may be linked to participation in post-marketing research projects.

6. To promote implementation of **gainsharing schemes** by regional health systems. To this end, it is proposed to inform the Ministry of Finance (Hacienda) on the need and benefits of these measures and to share the outcomes of these experiences among all Autonomous Communities within the Interterritorial Council of the Spanish national health system.

7. **To urge** Scientific Societies, Health Technology Assessment Agencies and Health Services to **update the therapeutic strategies included in the Clinical Practice Guidelines when a new biosimilar molecule is introduced**.

8. To urge the **Spanish Agency of Medicines and Medical Devices (AEMPS) to make a pronouncement on the safety of exchanging biological molecules** in order to promote issuing of recommendations by the **health administrations on the use of biosimilars** in naïve patients and chronic treatments, and on how to manage the switch of biological drugs in a consensual manner among experts with involvement of the patient.

9. To encourage the **development and publication of studies on health outcomes for biosimilars** so as to increase the confidence of healthcare professionals in biosimilar use.

10. To extend the use of the **framework agreement** as a procurement procedure with supplier approval upon market entry of a biosimilar.

11. To evaluate the **implementation of measures that promote prescription of biosimilars within primary health settings** in those therapeutic areas for which there are biosimilar biological molecules on the market.

12. **Outreach campaigns on biosimilars aimed at patients** conducted by national and regional organizations accredited for this purpose.

13. To involve the **Scientific Societies in the generation and dissemination of content through organized and protocolized training programmes** aimed at professionals.

14. ***Through health schools, and with the participation of patients' organizations and Scientific Societies***, to develop **training programmes for patients** that may contribute to the implementation of shared decision-making between clinician and patient.

Annex I. Methodology

As a starting point, a preliminary work proposal was prepared, consisting of a set of recommended reading and references, as well as a questionnaire that was sent to group members to gather their opinions and suggestions.

After analysing the information received, a meeting was held to share the proposals made by the working group, after which the first draft of the document was prepared for consensus by the expert panel.

This first draft was sent to group members and discussed at a second meeting, resulting in the preliminary version of a document where proposals for action are organized around four thematic sections:

- Section 1: Research, development and manufacturing of biosimilars
- Section 2: Use of biosimilars within the Spanish national health system
- Section 3: Public procurement and dispensing of biosimilars
- Section 4: Training and dissemination of knowledge on biosimilars.

This preliminary version has been revised by the working group, which has issued as many comments as deemed necessary. As a result of these revisions, the expert panel has reached an agreement on the proposals for action included in this document.

Annex II. Expert panel

In order to implement the actions described above, a multidisciplinary working group including the following experts was formed:

- **Manuel Barreiro**, President of GETECCU (Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa)
- **Concepción Carmona**, Deputy Director of Pharmaceutical Management at SES (Servicio Extremeño de Salud)
- **Olga Delgado**, President of SEFH (Sociedad Española de Farmacia Hospitalaria)
- **Mónica Elio y José Luis Baquero**, representing the FEP (Foro Español de Pacientes)
- **Jaime Espín**, Professor at EASP (Escuela Andaluza de Salud Pública)
- **Joaquín Estévez**, President of Fundación SEDISA (Sociedad Española de Directivos de la Salud)
- **Antón Fernández**, Healthcare Director of La Coruña's University Hospital Complex
- **Nieves Martín Sobrino**, Technical Director of Pharmaceutical Assistance at SACyL (Castilla y León Health Service)
- **Ángel Mataix**, President of SEFAP (Sociedad Española de Farmacéuticos de Atención Primaria)
- **Marta Morado**, Representative of SEHH (Sociedad Española de Hematología y Hemoterapia)
- **César Rodríguez**, Representative of SEOM (Sociedad Española de Oncología Médica)
- **Juan Carlos Valenzuela**, regional pharmacy coordinator of SESCAM (Servicio de Salud de Castilla-La Mancha)
- **Emilio Vargas**, Vice-President of SEFC (Sociedad Española de Farmacología Clínica)
- **José Manuel Ventura**, Chief Executive Officer of Pharmacy and Medical Devices of Generalitat Valenciana

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